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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,039	08/06/2002	Bonnie Davis	U 013729-7	8014

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EXAMINER	
MCMILLIAN, KARA RENITA	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
01/21/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/980,039	DAVIS, BONNIE	
	Examiner	Art Unit	
	KARA R. MCMILLIAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-22* is/are pending in the application.

4a) Of the above claim(s) *4-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 12-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 1, 2008 has been entered.

Response to Amendment/ Arguments

No amendments to the claims have been filed. Claims 3, 11, 23 and 24 are canceled. Claims 4-10 are withdrawn. Claims 1, 2, and 12-22 are presented for examination.

Applicant's arguments filed December 1, 2008, with respect to the rejection of claims 1-2 and 12-22 under 35 USC 103 over Saiko et al. in view of Davis et al. have been fully considered and are persuasive. As such said rejection has been withdrawn.

Applicant's arguments filed December 1, 2008 with respect to the rejection of claims 1-2 and 12-22 under 35 USC 103 over Walles et al., in view of Yorke et al., Trubnikova et al., and Davis et al. have been fully considered but they are not persuasive.

Applicants argue that the instant application claims compounds having central activity and that these compounds would not be the compounds of choice for local action on the ovaries. Walles et al. teach studies involving the direct application of acetylcholine to the ovaries. Applicants further argue that the compounds claimed in Davis et al. for the treatment of Alzheimer's disease would have central activity and there is no reason to assume that these compounds would result in a local increase in acetylcholine levels in the ovaries.

These arguments are found not persuasive since the instant application claims a method of failure of ovulation comprising the administration of acetylcholinesterase inhibitors such as analogs of galanthamine, having a central effect. Davis et al. was supplied to show that it was known that the galanthamine analogs claimed in the instant invention are acetylcholinesterase inhibitors capable of increasing acetylcholine levels. Davis et al. teach that it is known that inhibition of acetylcholinesterase activity will increase acetylcholine levels (see column 7 line 44-48). Claims 1-20 of Davis et al. claim a method of inhibiting acetylcholinesterase activity (in general) in a patient comprising the administration of various galanthamine analogs. While Davis et al. do teach that the compounds must have central activity for the treatment of Alzheimer's disease (as Applicants have pointed out), Davis et al. do not teach that the compounds must only have central inhibition of acetylcholinesterase activity or central increases in acetylcholine levels. Since Davis et al. claim the inhibition of acetylcholinesterase activity in general comprising the administration of various galanthamine analogs, one of ordinary skill in the art would be motivated to administer galanthamine analogs to

inhibit centrally acting as well as locally acting acetylcholinesterase activity in order to increase acetylcholine levels either centrally or peripherally.

Applicants further argue that egg extrusion would not solve the problems of failure to ovulate in humans. This arguments are found not persuasive since said disclosure of the prior art references meet the limitations claimed in the instant application. Applicants claim a method of treating the failure to ovulate in a human patient comprising the administration of acetylcholinesterase inhibitors. Ovulation is the extrusion of a mature egg from the ovary. Thus since the recited prior art references teach that acetylcholine causes the contraction of human follicles, and contraction of follicles causes the extrusion of an egg from the follicle, or ovulation, the claims of the instant application are rendered obvious.

Applicants further argue that it is not clear that muscle stimulation alone could cause extrusion of egg follicles. This argument is also found not persuasive sine the prior art references, Trubnikova et al. and Yorke et al. both teach that muscle contraction is necessary to expel an egg from the follicle.

For the reasons stated above and for the reasons of record the rejection of claims 1-2 and 12-22 under 35 USC 103 over Walles et al., in view of Yorke et al., Trubnikova et al., and Davis et al. is maintained. A modified rejection for better clarification is reproduced below. A new rejection of claim 12 under 35 USC 112 is detailed below.

This action is made **non-final**.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 recites the limitation "N-methyl group" in line 11 of the claim. There is insufficient antecedent basis for this limitation in the claim. To overcome said rejection, Applicant should modify claim 12 by replacing "methyl" in line 3 of claim 12 with "N-methyl."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2 and 12-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walles et al. (1974, European Journal of Obstetrics and Gynecology and Reproductive Biology, 4/1 supplement, pages S103-S107) in view of each of Yorke et al. (1980, Biology of Reproduction, Volume 22, pages 897-912), Trubnikova et al. (1989, Ontogenez, Volume 20, No. 5, pages 532-542, relying on English abstract), and Davis et al. U.S. Patent No. 6,150,354.

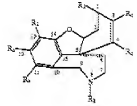
Claims 1-2 and 12-21 of the instant application claim a method of treating the failure of ovulation in a human patient comprising the administration of an acetylcholinesterase inhibitor such as analogs of galanthamine which have a central effect and thereafter determining whether a normal follicular response has been obtained and deciding further administration of the compound based on the results.

Walles et al. teach that acetylcholine causes contraction in human and cow follicles (see page S107 and figure 8 on page S106). Walles et al. does not specifically teach the administration of an acetylcholinesterase inhibitor or that contraction of follicles induces ovulation.

Yorke et al. teach that muscular contraction is associated with the expulsion of the egg from the follicle in vertebrates (see abstract).

Trubnikova et al. teach that contraction of follicular epithelium cells resulted in the retraction of the egg envelopes.

Davis et al. teach analogs of galanthamine, particularly those wherein the methoxy and hydroxy groups are replaced by, for example carbamate groups, or the methoxy group is replaced by hydroxy (see abstract). Claim 2 of Davis et al. claims a method of inhibiting acetylcholinesterase activity comprising administering a compound of the following formula:



wherein R1 or R2 may be a hydrogen; hydroxyl; alkoxy of 1-6 carbon atoms; monoalkyl or dialkyl or aryl carbamate; etc. It is also noted that galanthamine, and specific alkyl carbamates are taught as acetylcholinesterase inhibitors (see column 29, line 35 to column 30, line 60). Davis et al. also teach that it is possible to increase acetylcholine levels by decreasing the amount or activity of the acetylcholinesterase (see column 7, lines 44-48).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to administer an acetylcholinesterase inhibitor of Davis et al. in order to induce ovulation because (1) Davis et al. teach that the inhibition of acetylcholinesterase causes an increase in acetylcholine; (2) Walles et al. teach that acetylcholine causes the follicles to contract; and (3) both Yorke et al. and Trubnikova teach that the contraction of follicles is associated with the release of the egg (ovulation). One would have been motivated to administer the acetylcholinesterase inhibitors of Davis et al. because of an expectation of success in inducing release of the egg from the follicle.

It is noted that the claimed recitation of a central effect and a duration of action of from 1 to 100 hours is a property of the acetylcholinesterase to be administered. Since the same compounds are cited herein as obvious, the limitation is met. A compound and its properties are inseparable. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

It is further noted that the combined references have rendered obvious a treatment for the induction of ovulation. Accordingly, the combined references render

obvious the stimulation of the hypothalamic-pituitary-gonad axis since if ovulation is induced the hypothalamic-pituitary-gonad axis would necessarily have been stimulated.

Furthermore it is obvious to an ordinary skilled artisan to administer a drug and determine if the desired response is achieved. It is also obvious to an ordinary skilled artisan to determine if a condition has been treated or if further treatment is necessary. Said limitations as claimed in claim 1 of the instant application are routinely performed and not considered inventive. Thus said limitations are also rendered obvious.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Walles et al. (1974, European Journal of Obstetrics and Gynecology and Reproductive Biology, 4/1 supplement, pages S103-S107) in view of each of Yorke et al. (1980, Biology of Reproduction, Volume 22, pages 897-912), Trubnikova et al. (1989, Ontogenez, Volume 20, No. 5, pages 532-542, relying on English abstract), and Davis et al. U.S. Patent No. 6,150,354 as applied to claims 1-2 and 12-21 above and further in view of Polinsky (1998, Clinical Therapeutics, Volume 20, No. 4, pages 634-647).

Claim 22 of the instant application claim a method of treating the failure of ovulation in a human patient comprising the administration of an acetylcholinesterase inhibitor such as rivastigmine which have a central effect and thereafter determining whether a normal follicular response has been obtained and deciding further administration of the compound based on the results.

Walles et al. in view of Yorke et al., Trubnikova et al., and Davis et al. is as set forth above. Said references do not teach the acetylcholinesterase inhibitor rivastigmine.

Polinsky teaches that rivastigmine is an acetylcholinesterase inhibitor with brain-region selectivity and a long duration of action (see abstract). Polinsky further teaches that rivastigmine inhibits acetylcholinesterase mainly in the central nervous system with some inhibition in the peripheral (see abstract and page 639).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to administer the acetylcholinesterase inhibitor, rivastigmine as taught by Polinsky in order to induce ovulation because (1) Davis et al. teach that the inhibition of acetylcholinesterase causes an increase in acetylcholine; (2) Walles et al. teach that acetylcholine causes the follicles to contract; and (3) both Yorke et al. and Trubnikova teach that the contraction of follicles is associated with the release of the egg (ovulation). One would have been motivated to administer rivastigmine because of an expectation of success in inducing release of the egg from the follicle. Thus claim 22 is rendered obvious.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KARA R. MCMILLIAN whose telephone number is (571)270-5236. The examiner can normally be reached on Monday-Thursday from 8:30 am- 6:00 pm and every other Friday from 8:30 am- 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kara R. McMillian/
Examiner, Art Unit 1617

KRM

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617